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A Method for the Preparation of 2-(indol-3-ylmethyl)piperidines.

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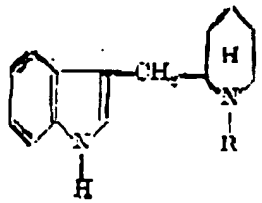
The present invention concerns a method for the preparation of 2-(indol-3-ylmethyl)piperidines. These preparations have been found to have interesting pharmacological properties which make them important in the preparation of drugs. They have a uterus-contracting effect.

These new compounds can be represented with the following formula:



Where R indicates hydrogen or an alkyl group, preferably a methyl group.

For example, preparation of these compounds may be carried out using the synthesis method according to Ladenburg (Roman numerals refer to the formula sheet).

In order to obtain the compound in which R = H, i.e., 2-(indol-3-ylmethyl)piperidine (III), isatin (I) is condensed with α-picoline, thus obtaining 3-(pyrid-2-ylmethyl)-3-hydroxyoxindole (II). It is now possible to reduce Compound II directly into Compound III using a metal and an alcohol, i.e., sodium and butanol. During this process, water is evidently split off, and the resulting double bond is involved in the reduction process. To the extent that this pyridylmethylidene intermediate product is already directly formed during condensation, it can naturally also be directly used as is for further reduction.

For preparation of compounds in which R represents an alkyl group, Compound III (i.e., with R = H) may be taken as a starting substance and directly alkylated on the nitrogen atom. In preparing the alkylated compound, however, it has been found to be advantageous to carry out reduction with substances such as sodium and butanol on quaternary alkylpyridinium halides derived from Compound II, and preferably on iodides. These compounds may be obtained from II through reaction with an alkyl halide, particularly an alkyl iodide.

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The quaternary alkylpyridinium halides obtained in this manner are as shown in Formula IV. During reduction, e.g., with sodium and butanol, compounds are therefore produced in which R = alkyl, as shown in Formula V.

The reduction of Compound IV described above may also be carried out by a stepwise process in which the pyridine nucleus is first catalytically hydrogenated, e.g., with platinum black as a catalyst, and a compound is then obtained as an intermediate product as shown in Formula IVa. This compound can then be converted, e.g., with sodium and butanol, into Compound V in the manner described above.

The invention is described in further detail in the following examples.

Example I

3-(Pyrid-2-ylmethyl)-3-hydroxyoxindole (II)

A mixture of 12 g of isatin and 24 cm³ of picoline is boiled for 4 hours, after which the excess picoline is distilled off under reduced pressure. The crystalline residue is suspended in chloroform, and the suspension is agitated twice with 80 and 20 cm³ respectively of N HCl. Following filtration, ammonia is carefully added to the acidic solution to a pH of 7. A small amount of tar-like material is first precipitated, this is removed, and the reaction product is then precipitated in the form of a yellow deposit (yield after drying at 100°C: 14.5 g; melting point 171-173°C). This product may be used for the following reactions without further purification.

The substance is obtained by recrystallization from ethanol in a colorless form with a melting point of 172-174°C (decomposition with red coloration).

Example II

2-(Indol-3-ylmethyl)piperidine (III)

74 g of sodium is added within 2 minutes with vigorous

stirring to a boiling solution of 12 g of the compound obtained according to Example I in 750 cm^3 of dry butanol.

After a short time, sodium butoxide is precipitated, and this substance is maintained in solution by adding an additional 250 cm^3 of butanol. After all of the sodium has disappeared, the reaction mixture is rapidly cooled and diluted with 1 l of water. The butanol layer is removed, and the strongly alkaline water layer is extracted by shaking twice with ether. The butanol is removed under reduced pressure and the residue is added to the ether solution.

This substance is then washed with water and extracted by shaking with dilute hydrochloric acid. After the acidic solution has been made basic, the reaction product, which is deposited in the form of an oil, is taken up in ether. After removal of the ether, the residue is dissolved in 20 cm^3 of warm benzene, from which solution the desired product is crystallized on cooling in the form of needles, with a yield of 2.6 g and a melting point of 156-157°C.

Example III

Methiodide of 3-(pyrid-2-ylmethyl)-3-hydroxyoxindole
(IV; R = $-CH_3$; Hal = I)

18.7 g of the product obtained by the method of Example I is suspended in a mixture of 60 cm^3 of methanol and 20 cm^3 of methyl iodide. The mixture is boiled for 20 hours. After cooling, 19.2 g of a light-yellow reaction product is crystallized out of the clear solution, and a second crystallizate can be obtained by boiling down the original solution (approximately 3.9 g). The combined products yield 19.3 g of the purified compound on recrystallization from ethanol. Melting point 160°C (cloudy, red coloration).

Example IV

3-(N-Methylpiperid-2-ylmethyl)-3-hydroxyoxindole
(IVa; R = $-CH_3$).

12 g of the product obtained according to Example III is suspended in 175 cm^3 of methanol, and it is then catalytically hydrogenated at atmospheric pressure and room temperature with 300 mg of platinum oxide as a catalyst by the Adams method.

Over a period of 4 hours, 3 mol of H_2 is taken up, after which the product does not consume any more H_2. After filtration, the methanol is boiled off under reduced pressure, and the desired reaction product is directly taken up in 250 cm^3 of butanol for further reaction. This method is preferred because the product of partial reduction is quite unstable and breaks down quite readily into isatin and 1,2-dimethylpiperidine.

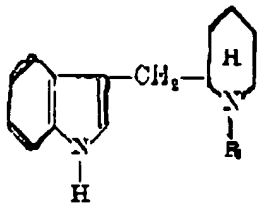
Example V

2-(Indol-3-ylmethyl)-N-methylpiperidine
(V: R = $-CH_3$)

The butanol solution obtained according to Example IV is brought to a boil, after which 20 g of sodium is added at an extremely rapid rate while stirring intensely. After the sodium has dissolved, the solution is diluted with 250 cm^3 of water with cooling, and the reaction mixture is processed as described in Example II. In this manner, one obtains 3.8 g of a thick syrup as a basic fraction which usually cannot be caused to undergo direct crystallization. The desired base is precipitated as a picrate (melting point 169-171°C). After decomposition of the picrate with lye, the base is taken up in ether, the ether is boiled off, and the residue is dissolved in benzene. The desired product is obtained from this in crystalline form (2 g; melting point 113-114°C; hydrochloride: melting point 228-230°C).

Claims

1. A method for the preparation of pharmacologically active compounds in which compounds having the general formula



where R represents hydrogen or an alkyl group, are prepared by a method which is known for such compounds.

2. The method of Claim 1, in which R is a methyl group.

3. The method of Claim 1, in which α-picoline is condensed with isatin and the intermediate product obtained is reduced with an alkali metal and an anhydrous alcohol.

4. The method of Claim 3, in which reduction is carried out using sodium and butanol.

5. The method of Claim 1, in which the compound in which R = H is alkylated by a known method.

6. The method according to Claim 1 or 2, in which the intermediate product of condensation of α-picoline with isatin is alkylated with a compound having the general formula of R-halogen, and the product obtained is then reduced in one or two steps.

7. The method of Claim 6, in which the condensation product is treated with an alkyl iodide.

Application No. 165229

1 page of drawings attached.